Scientific and Technical Principles for Fixed Dose Combination Drug Products for the treatment of HIV/AIDS, Malaria and Tuberculosis

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Scientific and Technical Principles for Fixed Dose Combination Drug Products

HIV/AIDS, tuberculosis, and malaria are the foremost infectious disease threats to public health that the world faces today and are the focus of many global initiatives. Combination therapy is considered to be essential in the treatment of these diseases and in the prevention of drug resistance.

From a public health perspective, an important approach to addressing the management of HIV/AIDS, tuberculosis and malaria has included the development of fixed dose combinations (FDC) of individual components administered together in one dosage form. Among others, FDCs simplify treatment regimens, improve convenience of use and patient adherence, facilitate the implementation of interventional programs, and potentially limit the development of drug resistance. The importance of combination therapy is not unique to AIDS/HIV, malaria and tuberculosis. Combination therapy is also used in the treatment of infections other than those listed above, as well as in non-infectious diseases such as hypertension, diabetes and epilepsy. However, the scope of this document is to concentrate only on combination therapies to be used for treating HIV/AIDS, tuberculosis and malaria.

Notwithstanding the benefits described above, there are challenges related to the development and use of FDCs such as dose titration of the individual components, the interplay of adverse effects, allergies to one or more of the components, and complex pharmacokinetic (PK) or pharmacodynamic profiles.

It should be noted that the risk/benefit assessments for FDCs may have to take into consideration the differences in anticipated patient populations, and that decision-making may vary between the different national drug regulatory authorities.

Currently there are a limited number of FDCs available for the management of HIV/AIDS, malaria and tuberculosis in children, and as these diseases also commonly affect children, the development of paediatric formulations of FDCs should be encouraged. Furthermore, to facilitate treatment of these diseases, additional FDCs need to be developed for all age groups, including for children.

The development of FDCs may vary depending on their individual active components and on the indications that they target. Currently, there are no detailed uniform principles, guidelines or international standards addressing the development of FDCs and their potential benefits or possible disadvantages in treating these diseases. However, the World Health Organization (WHO) is in process of developing a more detailed guideline on FDCs.

PURPOSE

The purpose of this document is to facilitate and promote the development of FDCs, by both innovator and generic pharmaceutical manufacturing companies. It provides principles to be taken into account when considering, developing and evaluating FDCs. These principles focus on scientific and technical aspects of the efficacy, safety, and quality of FDCs intended for the treatment of HIV/AIDS, tuberculosis and malaria.

This document is not a therapeutic or regulatory guideline. It is, however, intended to increase the general awareness of scientific and technical issues related to the development of FDCs. It does not address specific issues such as the procurement and distribution of specific products. Throughout this document references are made to publications from WHO, national and regional regulatory authorities, and other appropriate publications that are listed in a reference section at the end of the document. Reference documents are intended to provide additional information. However, it should be noted, that references identified do not represent a comprehensive list of all references and may be supplemented with other appropriate documents.

CONSIDERATIONS

In the development or evaluation of FDCs, it is necessary to take three factors into account:

- The safety and efficacy of the individual active components
- The safety and efficacy of the simultaneous use of the individual active components (multi drug regimen)
- The possible interaction between active components derived from a multi drug regimen when they are formulated into an FDC.

The following considerations generally apply when determining whether active components are suitable for a multi drug regimen, and hence also for FDCs. The medical and scientific rationale should support the simultaneous use of more than one active component in at least one of the following ways:

- Increased efficacy (additive or synergistic)
- Reduced toxicity
- Limiting the development of pathogen resistance
- Boosting of drug levels.

Additionally, FDCs have some important advantages over multi drug regimens, such as:

- Improved adherence
- Convenience of use
- Reduced pill burden and/or simpler treatment regimens
- Facilitating logistics of procurement, distribution and dispensing.

To develop a practical FDC dosage regimen, it is necessary to choose constituent active components that have suitable pharmacokinetic and physiochemical properties. Several factors need to be considered:

- Combining active components with different pharmacokinetic characteristics may present problems. For example, combining antimicrobials with short and long elimination half-lives may result in the emergence of drug resistance where a single component persists in

the absence of the companion drug(s), particularly in the case of long term treatment. It may be possible to address differences in pharmacokinetics by modification of formulations.

- Conflicting effects of food on the bioavailability of the components might complicate a dosing strategy.

- The components used in FDCs should be chemically and physically compatible, unless formulation techniques have been demonstrated to overcome any incompatibility.

Paediatric FDC formulations often differ from adult FDCs, and special consideration is needed concerning issues such as stability, palatability, dosing (frequency, mg/m^2, mg/kg), toxicity (e.g., excipients and degradation products) and food requirements.

This document will describe the principles of FDC development in relation to the following four scenarios:

Scenario 1

A new FDC product developed as a generic bioequivalent to an existing FDC.

Scenario 2

A new FDC product developed by combining active components that are already well studied and for which the simultaneous use of all the individual active components in a multi drug regimen has been well characterised as safe and effective. The dosage regimen of the components given individually in a multi drug regimen and the dosage regimen of the FDC are the same.

Scenario 3

A new FDC product developed from individual components that have a well-characterised safety and efficacy profile on their own, but the efficacy and safety of their simultaneous use in a multi drug regimen is not well established; or an FDC developed using two or more well-characterised individual components of an established multi drug regimen when the dosing regimen of the FDC is novel.

Scenario 4

A new FDC product developed by incorporating one or more new molecular entities.

Microbiology

Scenarios 1, 2

Generally, no microbiologic evaluations are needed, unless the new FDC is intended for a different geographic area with a different pathogen and/or resistancy pattern.

Scenarios 3, 4

Microbiologic evaluations may be needed to determine the advantage of multi drug regimens or FDCs over individual active components against a given pathogen. Such microbiologic studies may be needed to motivate the selection of appropriate entities for combined use, and to evaluate the advantage of the multi drug regimen over individual active components, when clinical trials of monotherapy are inappropriate or unethical. The following types of data may be important and should be obtained from studies performed to accepted standards:

- Characterization of microbiologic activity in vitro and in vivo against laboratory strains and clinical isolates of the targeted pathogens including those in the relevant geographic regions
- Characterization of microbiologic activity in appropriate animal models of infection with the targeted pathogens
- Characterisation of the mechanism by which the active ingredients exhibit additive or synergistic microbiologic activity against the targeted pathogens
- Investigation of potential antagonistic effects between the active components
- Investigation of the potential for development of resistance of target pathogens in vitro and in vivo.
- Where there are concerns about sub-therapeutic trough levels, investigation of microbiologic activity at anticipated human C_{min} concentrations might be needed. In such cases, C_{min} should be evaluated in human steady-state PK studies.

Scenarios 1, 2

- Non-clinical pharmacology and toxicology studies are generally not needed, as long as internationally acceptable excipients are used, and the impurities profile does not significantly deviate from the reference product.

Scenario 3

- For FDCs of two or more licensed products, the need for nonclinical pharmacology or toxicology studies should be considered on a case-by-case basis. Generally, a bridging toxicity study should be considered if the combination is novel, or if the dose is higher than previously characterised and accepted. The design of the bridging study will depend on the individual components of the FDC. In such studies, consideration should be given to the dose ratios to be used in nonclinical studies versus the ones in clinical use and to the systemic exposure in animal versus man.
- Additional nonclinical studies may be requested if the proposed indication involves longer treatment duration than is currently licensed for one or more of the active components in the FDC.
- Additional non-clinical studies may be requested based on the outcome of the bridging study or if there is potential for drug interactions or overlapping toxicity.

Scenario 4

- A combination of one new molecular entity—for example, a new active component not previously licensed for medicinal use in humans—with one or more licensed active components requires a complete nonclinical evaluation (including genotoxicity and reprotoxicity studies) of the new molecular entity. In addition, investigation of the toxicokinetics and a bridging toxicity study for the FDC may be needed. Alternatively, a complete non-clinical pharmacologic and toxicologic evaluation of the FDC (instead of the new molecular entity alone) may be considered as an option.
- If more than one new molecular entity is included in an FDC, a complete nonclinical evaluation (including genotoxicity and reprotoxicity studies) of each new single entity and an appropriate bridging study for the FDC are required. The design of the bridging study depends on the individual entities of the FDC and the proposed conditions of use.
- Additional nonclinical studies may be needed based on the outcome of the bridging study or if there is potential for drug interactions or overlapping toxicity between the new and already licensed entities of the intended FDC.

All Scenarios

For all scenarios, additional nonclinical studies may be needed if new concerns are raised from nonclinical or clinical information.

Scenario 1

- A properly designed study will need to demonstrate bioequivalence (BE) between the FDC and an adequate reference product. For details see "the Bioequivalent FDC Products section" below.

Scenario 2

- A properly designed study will need to demonstrate bioequivalence between the FDC and the individual active components given together. For details see the "Bioequivalent FDC Products section" below.

- The advantage of the combination may differ depending on the individual active components and the indication for use as described previously. The rationale for the simultaneous use of the individual active components in a multi drug regimen (and therefore in the proposed FDC) must be justified. Each active component must be shown to contribute an advantage, when incorporated into the multi drug regimen or FDC at the relevant doses. This may generally be demonstrated by means of a systematic review of the literature and/or other already existing data.

Scenario 3

- The potential for favourable or unfavourable interactions between the components should be investigated in appropriate PK and pharmacodynamic studies.

- For a novel FDC (where a corresponding multi drug regimen has not already been established), the rationale for the simultaneous use of the individual active components generally needs to be justified by means of adequate comparative clinical studies. Such clinical studies should convincingly demonstrate the contribution to the efficacy and/or safety of each active component incorporated into the combination at the proposed doses.

- When a novel FDC involves a change in the dose regimen of a previously characterised multi drug regimen or FDC, comparative clinical studies should be performed, demonstrating at least equal efficacy and safety of the new dosing regimen compared to the previously used regimen.

- In situations where comparative clinical trials are not feasible, for example when monotherapy is not acceptable, an aggregate of clinical and nonclinical data may be substituted. Such data may include:

    - historical clinical data on the components used alone at comparable doses / at comparable exposure as in the proposed FDC

    - bridging PK data, where applicable

- non-clinical pharmacology and/or toxicology data
- in-vitro microbiologic data

- Clinical trials should demonstrate that the proposed FDC is statistically either non-inferior, equivalent, or superior compared to recognised treatment for the proposed indication. The reason for the choice of statistical hypothesis needs to be specified in the study protocol and the chosen option should be appropriate to the nature of the comparator and the scientific objective. For example, if a novel three-drug FDC is compared to an existing FDC containing two of the active components, superiority should be shown. If an FDC is compared to a recognised treatment containing different active components, at least non-inferiority should be shown.

- Combining the components of the proposed multi drug regimen into one product should not compromise the overall risk-benefit profile.

- When there is potential for a drug interaction or overlapping toxicity, preclinical toxicity studies, clinical safety studies and dose ranging studies may be needed before embarking on clinical efficacy studies.

Scenario 4

- A comprehensive clinical development program is needed.

General Considerations for Clinical Studies "Selection of Endpoints in Clinical Trials" (Scenarios 3 and 4)

- In clinical safety and efficacy studies, comparators or comparator regimens should represent the recognised treatment for the indication in question. Because reliable performance of the comparator pharmaceutical product is crucial in determining the safety and efficacy of new FDCs or combination regimens, these comparators should be licensed products, preferably innovator products or licensed products whose safety, efficacy, and quality parameters have been well established and independently vetted by a recognised drug regulatory authority.

- Unapproved or novel combinations should be avoided as comparators, as they may introduce new toxicities and complicate the evaluation of safety and efficacy.

- Individual components that are being considered for inclusion in an FDC should have a well-established risk-benefit profile in the target population when used according to the recommended dosing regimens. Consideration should be given to ethnic, environmental, co-morbid, and nutritional variations between populations, when scientifically appropriate.

- The protocols should clearly state whether non-inferiority, equivalence or superiority is the objective of the studies.

Selection of Endpoints in Clinical Trials

- Clinical and microbiological endpoints including treatment duration should be selected that are relevant for the indication. Accepted guidelines, where available, should be used, some of which are provided in the reference section below.

- The follow-up period in clinical trials should be long enough to allow:

  - a realistic assessment of efficacy,

  - where applicable, an assessment of the risk of relapse after cessation of therapy,

  - an adequate assessment of late-appearing adverse events.

FDCS AND POSTLICENSING RESPONSIBILITIES

Postmarketing surveillance is a shared responsibility between physicians, patients, other healthcare providers, manufacturers and drug regulators. Capacity building may be needed for postmarketing surveillance where such systems are underdeveloped or lacking.

In addition to the postmarketing safety and efficacy concerns, which are typical of all medicinal products, FDC products used in the treatment of HIV/AIDS, tuberculosis, and malaria have specific postmarketing issues that may need to be investigated. These include:

- Adverse events caused by one of the components that change the risk-benefit profile of the combination

- Additive or synergistic toxicities

- Change in the resistance profile of pathogens or the relative prevalence of different pathogens

- Diminishing efficacy

For scenarios 1 and 2 surveillance (spontaneous reporting) based on national or regional standards would generally be sufficient.

For scenarios 3 and 4 prospective active surveillance, such as a concrete pharmacovigilance plan, may need to be considered under certain circumstances (e.g. in case of anticipated safety concerns).

BIOEQUIVALENT FDC PRODUCTS

This section of the document is confined to those principles pertaining to FDC products in Scenarios 1 and 2 and should be considered in conjunction with existing national and international BE guidelines.

Safety and efficacy of FDC products not only depend on bioequivalence, but may also depend on the inactive ingredients (see the sections on Clinical Safety and Efficacy, and Quality).

BE studies are performed to show that a multisource drug product is interchangeable with the innovator's version, and that it can be administered with the expectation that it will be therapeutically equivalent. In a BE study, PK endpoints are used for systemically active oral dosage forms.

The principles of Good Clinical Practise should be used when carrying out any BE study, and appropriate guidelines should be consulted. See the World Medical Association Declaration of Helsinki, posted at *www.wma.net/e/policy/b3.htm*, and the Reference Documents section.

Study Design

For an FDC product from Scenario 1, the reference products should be preferably the innovator FDC product or chosen from licensed products whose safety, efficacy, and quality parameters have been well established and independently vetted by a recognised drug regulatory authority.

For a new fixed-dose combination product from Scenario 2 an appropriate study design would be a randomised two-way crossover design. One arm receives the fixed-dose combination, and the other arm receives the same dose of the active ingredients, each provided simultaneously as a separate licensed drug product. The separate licenced drug products should preferably be the innovator products or be chosen from licensed products whose safety, efficacy, and quality parameters have been well established and independently vetted by a recognised drug regulatory authority.

Crossover studies are conducted with a washout period (generally at least five half-lives in duration) between each treatment to ensure that the effects of the treatment are entirely eliminated before administration of the next treatment. For an FDC product, the half-life chosen to determine the washout period between treatments should be the one for the active pharmaceutical ingredient (API) with the longest half-life. For drugs with a highly variable half-life, the upper limit of the range of possible half-lives should be used to determine the washout period.

For long half-life drugs, where the washout exceeds four weeks, a parallel study design may be used.

Subjects

The number of subjects is determined by the error variance associated with the drug product to be studied, estimated either from a pilot experiment, previous studies, or published data. The error variance chosen should be the one for the most variable API in the FDC product.

The number of subjects should not be less than 12; in most cases, 24 to 36 subjects will be adequate. Conducting a BE study which includes both male and female subjects or which compares drugs with highly variable PKs, an increased number of subjects may be needed.

For bioequivalence testing of pediatric formulations, adult volunteers are generally used.

Relevant PK Parameters

The PK parameters to be reported and assessed are those which would normally be reported and assessed in a BE study, and are those which would normally be required of each API if it were in the formulation as a single entity.

Bioequivalence of two products in a study with PK endpoints is determined by measuring blood or plasma drug concentrations over time to calculate the parameters characterising rate and extent of drug absorption.

Under certain circumstances, bioequivalence may need to be demonstrated by calculating the appropriate PK endpoints from urine samples.

Sampling times should be chosen such that the concentration profile is adequately defined to allow calculation of the relevant PK parameters for all APIs in the FDC product.

- For drugs with a long half-life (>24 hours) the sampling should cover a minimum of 72 hours unless 80 percent of the known AUC $_{0-\infty}$ is recovered before 72 hours. Truncation of the AUC to times other than 72 hours will require justification ensuring the absorption process is complete.

Bioanalytical Method Variation

All bioanalytical methods should be well characterised, fully validated, and documented, and state the method of validation in the protocol. Study reports should be provided to regional and national regulatory authorities according to their guidelines. See guidelines in the Reference Documents.

Statistical Analysis

Subject

The BE criteria should be met on each API in the FDC product.

The AUC and C_{max} data are log-transformed prior to statistical testing. The statistical tests are implemented using the analysis of variance procedure. A 90 percent confidence interval is calculated for AUC and C_{max}.

For AUC, the 90 percent confidence interval for the test to reference ratio of each drug of the test to reference formulation should lie within the acceptance interval of 80 percent to 125 percent.

The acceptance criteria for C_{max} must meet the criteria in existing national and international BE guidelines, as set out by the drug regulatory authority where the application for approval is made. The range used should be justified taking into account safety and efficacy considerations.

Evaluation of T_{max} data should be performed as per the existing national and international BE guidelines, as set out by the drug regulatory authority where the application for approval is made. If statistical methods are applied to T_{max}, nonparametric methods are recommended as the T_{max} does not show a normal or log-normal distribution.

Fasting and Fed Bioequivalence Studies

The requirement for fasting and fed BE studies for an FDC product should be based on the known PK and product labelling of all the API present in the FDC product. A waiver for either a fasting or fed study should be based on a sound scientific rationale.

Waivers for In Vivo Testing

In some circumstances, in vivo BE studies can be waived:

- When the drug product is the same dosage form but different strength, and is proportionally similar in its active and inactive ingredients to the strength on which BE testing has been conducted, an in vivo BE study of one or more strengths can be waived based on dissolution tests and an in vivo study on one strength, generally the highest strength.

- A BE study may not be required if a drug product is an oral solution at the time of administration provided that the following criteria are met:

    - The active substance should be in the same concentration and form as a currently approved drug product; and

    - The drug product should not contain excipients that may affect gastrointestinal transit or absorption of an active substance.

- A waiver may be considered under the current Biopharmaceutics Classification System guidance. See guidelines in the Reference Documents section.

Dissolution Testing

A discriminating dissolution method should be developed, with limits set, for each active pharmaceutical ingredient in a drug product. The dissolution method should be incorporated into the stability and quality control programs.

- Dissolution testing must ensure that the presence of two or more drugs does not affect the performance of the dissolution testing.
- For scenarios 1 and 2, multipoint dissolution profiles for both the test and reference products should be compared. Only the new FDC product is evaluated for scenarios 3 and 4.
- For biowaiver testing, multipoint dissolution profiles of both test and reference product across all strengths should be generated and compared for similarity.

QUALITY

The quality principles outlined below are critical to FDC products, including paediatric formulations, and should be used in conjunction with existing national and international quality and GMP guidelines for all APIs and pharmaceutical dosage forms. They are equally applicable in all four scenarios described in this document.

Active Pharmaceutical Ingredients

To ensure consistent quality in FDC finished products, APIs should be controlled for parameters such as impurities, particle size distribution, and polymorphism. See the Reference Documents section.

- Finished product manufacturers should use APIs from manufacturers acceptable to regulatory authorities. In addition, good trade and distribution practises should be followed.
- APIs with pharmacopoeial monographs may still need additional information because of different physiochemical properties, impurity profiles and use of organic solvents in their synthesis, as outlined in the International Conference on Harmonisation quality guidelines.
- APIs not subject to pharmacopoeial monographs should follow ICH quality guidelines, especially for stability, impurities and residual solvents.

Finished Product

- When considering FDC products, attention should be given to pharmaceutical development and manufacture, with an outline of the process-development principles of the formulation, as these products are technically more demanding than single component products.
- As part of pharmaceutical development it should be demonstrated that the individual ingredients are compatible with each other as well as the excipients and primary packaging materials used in the final dosage form.
- Drug content uniformity is considered essential for FDC finished products and should be addressed in the drug development process and the final process validation. This test should be designed to demonstrate

the uniformity of dose consistent with the overall performance of the product.

- Analytical methods that can distinguish each API in the presence of other APIs in the FDC should be developed and validated.
- Methods should also be developed to detect actual and potential degradation of products. These methods should be appropriately validated in accordance with national and international guidelines.
- To confirm consistency and uniformity in the FDC products, in-process controls are required to ensure that the formulations are mixed properly throughout the manufacturing process.
- Content uniformity of the finished dosage form, where appropriate, should be demonstrated by assaying for each active component in the final product.
- Suspensions and powders for suspensions should be controlled for sedimentation rate and resuspendability.
- Solutions should be examined for crystallisation and precipitation.
- Dissolution testing specifications should include all active components of the finished dosage form and utilise relevant media. See the Bioequivalent FDC Products section.

Stability

- Stability requirements have been well established in national and international guidelines. In view of the urgency of availability of FDC products, it may be possible to consider limited stability data at the time of filing, recognising that the required stability data package will be provided at a later date. In addition:
    - Stability studies should be designed with the geographic climate of the target market in mind.
    - Repackaging of bulk finished product will require stability studies in the bulk container and the final container closure system. Expiration dating is linked to the manufacturing date of the dosage form.
    - Methods that measure and indicate product stability should be developed.
    - Instructions concerning storage conditions should be labelled and clearly visible.
- Alternative accelerated stability studies may be considered on a case by case basis and must be accompanied with a sound scientific justification.

Packaging

Packaging should be selected to ensure the quality of the final product throughout its shelf life.

Repackaging of FDCs is discouraged. However, if repackaging is necessary, it should be in line with GMP principles as well as subject to appropriate release and control testing.

Inspections to Assure Compliance with GMPs

Manufacturing of FDCs must be done according to internationally recognised GMPs acceptable to the regulatory authority.

REFERENCE DOCUMENTS

The reference documents listed below are intended to provide additional information. However, it should be noted, that documents identified do not represent a comprehensive list of all references documents and may be further supplemented.

Nonclinical and Clinical

"Note for Guidance on Repeated Dose Toxicity," July, 2000. Committee for Proprietary Medicinal Products.
www.emea.eu.int/pdfs/human/swp/104299en.pdf

"Note for Guidance on Fixed-Dose Combination Medicinal Products," April 1996, Committee for Proprietary Medicinal Products/Efficacy Working Party/240/95.

"Note for Guidance for on the Clinical Development of Medicinal Products for Treatment of HIV Infection." March, 2003, Committee for Proprietary Medicinal Products, www.emea.eu.int/pdfs/human/ewp/063302en.pdf

"Points to Consider on Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products," July, 2000. Committee for Proprietary Medicinal Products/Efficacy Working Party/2655/99.
www.isap.org/1999/Uppsala/265599en.pdf

"Note for Guidance on Duration of Chronic Toxicity Testing in Animals," Nov. 1999. International Conference on Harmonisation. *www.ich.org*

"Dose-Response Information to Support Drug Registration," March 1994. International Conference on Harmonisation. *www.ich.org*

"Pharmacovigilance Planning, E2E," Nov. 11, 2003. International Conference on Harmonisation. *www.ich.org*

Guidelines for good clinical practice (GCP) for trials on pharmaceutical products", 1996, World Health Organization, Technical Report Series No. 850, 1995, Annex 3.
www.who.int/medicines/library/par/ ggcp/GCPGuidePharmatrials.pdf

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Bioequivalence

"Note for Guidance on the Investigation of Bioavailability and Bioequivalence," ommittee for Proprietary Medicinal Products, July 2001. *www.emea.eu.int/pdfs/human/ewp/140198en.pdf*

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"Progress in Essential Drugs and Medicines Policy," Anx 4: Multisource (Generic)Pharmaceutical Products: Guidelines on Registration Requirements and Interchangeability, 1996.*www.who.int/medicines/library/edm_general/annual_rep/prog98_99.pdf*

Guidance for Industry: "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System," August, 2000. U.S. Department of Health and Human Services, Federal Drug Administration, Center for Drug Evaluation and Research. *www.fda.gov/cder/guidance/3618fnl.htm*

Guidance for Industry: "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations," March 2003. U.S. Department of Health and Human Services, Federal Drug Administration, Center for Drug Evaluation and Research. *www.fda.gov/cder/guidance/3615fnl.htm*

Guidance for Industry: "Food-Effect Bioavailability and Fed Bioequivalence Studies," December, 2003. U.S. Department of Health and Human Services, Federal Drug Administration, Center for Drug Evaluation and Research. *www.fda.gov/OHRMS/DOCKETS/98fr/03-2214.htm*

Guidance for Industry: "Dissolution Testing of Immediate Release Solid Oral Dosage Forms," August, 1997. U.S. Department of Health and Human Services, Federal Drug Administration, Center for Drug Evaluation and Research. *www.fda.gov/cder/guidance/1713bp1.pdf*

Guidance for Industry: "Conduct, and Analysis of Bioavailability and Bioequivalence Studies, Part A: Oral Dosage Formulations Used for Systemic Effects," 1996. Health Canada, Health Products and Food Branch.

Quality

"Stability Testing of New Drug Substances and Products, Q1A (R2)," February, 2003. International Conference on Harmonisation, Harmonised Tripartite Guideline. *www.ich.org*

"Stability Data Package for Registration Applications in Climatic Zones III and IV, Q1F," February 2003, International Conference on Harmonisation. *www.ich.org*

"Good Manufacturing Practise Guide for Active Pharmaceutical Ingredients, Q7A," November 2000. International Conference on Harmonisation. *www.ich.org*

"Impurities in New Drug Substances, Q3A(R)," February 2002. International Conference on Harmonisation. *www.ich.org*

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"Good Manufacturing Practices for Pharmaceutical Products: Main Principles," 2003. World Health Organization, Technical Report Series No. 908, Annex 4. *www.who.int/medicines/library/qsm/trs908/trs908-4.pdf*

"Good Trade and Distribution Practices for Pharmaceutical Starting Materials," 2003. World Health Organization, Technical Report Series No. 917, Annex 2.
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www.who.int/medicines/strategy/quality_safety/annex5_trs863.doc

Guidelines for stability testing for pharmaceutical products containing well established drug substances in conventional dosage forms", update, 2003. World Health Organization, Technical Report Series No 908.
www.who.int/medicines/strategy/quality_safety/stqsmnorms.shtml

CPMP "Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products," December, 2003. Committee for Proprietary Medicinal Products. CPMP/QWP/122/02, rev1.
www.emea.eu.int/pdfs/human/qwp/012202en.pdf

"Guidelines on packaging for pharmaceutical products", 2002. World Health Organization,
Technical Report Series No 902, 2002.
www.who.int/medicines/strategy/quality_safety/trs902ann9.pdf)

Active Component: any component that provides pharmacological activity or has other direct effects on the diagnosis, cure, mitigation, treatment, or prevention of disease, or has effects on the structure or function of the body in man or in animals.

Active Surveillance: Active surveillance seeks to ascertain completely the number of adverse events via a continuous pre-organised process.

AUC: the area under the curve for the drug or metabolite concentration in plasma, serum, or whole blood against time.

Bioavailability: the rate and extent to which the active ingredients or active moieties are absorbed from the drug product and become available at the site of action, the treatment site, within the body. For drug products that are not intended to be absorbed into the bloodstream, bioavailability can be assessed by measurements intended to reflect the rate and extent to which the active components or active moieties become available at the site of action.

Bioequivalence (BE): the scientific, physiopharmacologic basis on which a test and a reference drug are compared or an FDC of active ingredients and the individual active ingredients administered simultaneously are compared. To be determined bioequivalent, the bioavailability of the two products must not differ significantly when the two products are given in the same dosages under similar conditions to the same person. Substitution of one product by a bioequivalent product should result in the same clinical safety and efficacy profile in the patient. It is important that those who substitute various products based on a finding of BE understand the definition of "not differ significantly," as that is the basis of the claim of BE for the product being substituted.

Bioequivalent FDC product: an FDC product that can be substituted in patient care for an innovator product. It has demonstrated bioequivalence to a referenced innovator product and completed manufacturing processes and controls. By following the innovator's administration instructions, the bioequivalent FDC product can be expected to have the same clinical safety and efficacy profile in patients as the innovator product. The bioequivalent FDC product can rely on the innovator product's clinical and preclinical safety and efficacy data and forgo a formal clinical safety and efficacy clinical testing program. These products, often produced by many different manufacturers, are sometimes referred to as multisource interchangeable products. In some jurisdictions these products are called generic products. However, because in other jurisdictions, the term generic does not include the critical concept of BE, the use of the term generic drug product in international documents is not recommended.

Bridging Toxicity Study: a limited nonclinical study that allows the assessment of the overall toxicity of a multidrug regimen or an FDC consisting of individual active components for which the toxicity is already well characterized at the dose level of interest. The design of such a study will depend on the existing knowledge of the toxicity and toxicokinetics of the individual components.

C_{max}: the observed maximum or peak concentration of a drug or metabolite in plasma, serum, or whole blood.

C_{min}: the minimum concentration of a drug measured between one dose and the next.

Efficacy: the desired effect of a drug on a disease condition. Efficacy must be established by substantial evidence, such as independently corroborated

evidence, usually from appropriately blinded well-controlled clinical trials, which demonstrate that the drug will have the effect claimed in the intended population according to predetermined statistical and clinical criteria.

Fixed dose combination product (FDC): a single product created by the combination of two or more active components in a single formulation, and in which each active component contributes to the benefit of the new product. FDCs are not simply two single, distinct products packaged together. Active ingredients can be pharmaceutical (i.e., chemical) or biologic in origin.

Innovator FDC product: the first licensed formulation of a new FDC product, generally as a patented drug, on the basis of original scientific documentation of safety, efficacy, and pharmaceutical quality.

Innovator product: the first licensed formulation of a new product, generally as a patented drug, on the basis of original scientific documentation of safety, efficacy, and pharmaceutical quality.

Licensed FDC product: an FDC for human use which has underlying clinical, preclinical, and manufacturing data that has been examined and vetted independently by government-recognised, competent drug regulatory authorities and meets required scientific and legal standards for authorised marketing in those jurisdictions. Also called "approved," "registered," or "authorised" products in some jurisdictions.

Monotherapy: using one drug for the treatment of a condition.

Multidrug Regimen: using more than one drug simultaneously for the same condition.

Multisource Product: Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

New Molecular Entity: an active pharmaceutical ingredient that has never been used in a marketed finished dosage form.

Pharmaceutical Equivalence: products that contain the same amount of the same APIs in the same dosage form and meet the same or comparable standards if they are administered by the same route. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients or the manufacturing process can lead to changes in dissolution and absorption.

Post-Marketing Surveillance: procedures implemented after approval, registration, or licensure of a drug for a given indication that is designed to provide information on the actual use of the drug for that indication and on the occurrence of related side effects. The surveillance usually involves survey techniques rather than controlled trials.

Quality: the ability of a product to consistently meet established physiochemical purity and potency standards based on adherence to adequate manufacturing process controls and recognised Good Manufacturing Practise. Manufacturing quality of the product is ensured by having in place robust systems to assure that products are manufactured according to established GMPs, including recognised validation practises that establish the product can be consistently manufactured from batch to batch.

Safety: a measure of the product's ability to cause the desired effect without harming the patient. As no drug is completely safe, a positive risk-benefit ratio needs to be established for the intended patient population based on nonclinical and clinical data (i.e., that the established benefits of the product

outweigh the known risks of the product when used as directed in the intended population).

Surveillance: spontaneous reports voluntarily reported either to pharmaceutical manufacturers, to national or regional pharmacovigilance centers, or to national regulatory authorities by healthcare professionals, other professionals, or consumers.

Stability: the drug product's resistance to changes in its physical, chemical, and microbiological properties over time in the market environment.

Statistical Equivalence: when the efficacy/evaluated effect of the investigational product does not differ substantially in either direction from the comparator. If two treatments are to be declared equivalent, then the two-sided $(1-\alpha)x100$ percent confidence interval should lie entirely within a prespecified interval (α is defined as the type I error of the test).

Statistical Non-inferiority: the efficacy / evaluated effect of the investigational product is not substantially inferior to that of the comparator. The lower bound of the $(1-\alpha)x100$ percent confidence interval around the observed efficacy / effect of the investigational product minus the observed efficacy / effect of the comparator product is greater than the prespecified limit (α is defined as the type I error of the test).

Statistical Superiority: when the efficacy / evaluated effect of an investigational product is better than that of the comparator. The lower bound of the $(1-\alpha)x100$ percent confidence interval around the observed efficacy / effect of the investigational product minus that of the comparator product is greater than zero (α is defined as the type I error of the test).

Systematic Review: an analysis of an existing body of evidence that addresses clearly formulated questions and uses systemic and explicit methods to identify, select and critically appraise relevant research using statistical or nonstatistical methods.

Therapeutic Equivalence: two products that in efficacy and safety are essentially the same and are pharmaceutically equivalent after administration in the same molar dose, as determined from appropriate bioequivalence, pharmacodynamic, clinical, or in vitro studies.

T_{max}: the time point after administration of the drug at which C_{max} is observed.

LIST OF ACRONYMS

ANOVA	analysis of variance
API	active pharmaceutical ingredient
AUC	area under the curve
BE	bioequivalence
CDER	Center for Drug Evaluation and Research
CPMP	Committee for Proprietary Medicinal Products
DHHS	United States Department of Health and Human Services
EWP	Efficacy Working Party
FDC	fixed dose combination
GMP	Good Manufacturing Practise
ICH	International Conference on Harmonisation
NIH	National Institutes of Health
PK	pharmacokinetic
WHO	World Health Organization

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